Aerobic exercise training improves autonomic nervous control in patients with COPD

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KEYWORDS
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Summary
Objectives: Autonomic modulation is adversely impacted in patients with chronic obstructive pulmonary disease (COPD). The purpose of the present investigation is to assess the effects of a 6-week aerobic exercise training program on autonomic modulation of heart rate in patients with COPD.

Methods: Forty patients of both sexes with moderate-to-severe COPD were randomly allocated to aerobic exercise training (PT, n = 20) or to usual care (Control, n = 20). The training program consisted of lower and upper limb stretching and 30 min of treadmill exercise, 3 times per week for a 6-week period. Physiological data during symptom-limited exercise testing and the six-minute walk test (6MWT) were assessed. In addition, R–R intervals were obtained at rest and during the 6MWT. Heart rate variability was analyzed by time (rMSSD and SDNN index) and frequency domains (high frequency — HF, low frequency — LF and HF/LF ratio).

Results: Peak oxygen consumption significantly improved in the training group only (p < 0.05). Moreover, the training group demonstrated significant improvements (p < 0.05) in blood lactate, minute ventilation, dyspnea at peak exercise, sympathetic activity, and parasympathetic activity at rest and during submaximal exercise. Lastly, a positive and significant correlation was found between change in 6MWT distance and rMSSD index (r = 0.65 and p = 0.001).

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Introduction

Cardiovascular autonomic neuropathy is a common consequence of chronic obstructive pulmonary disease (COPD).\textsuperscript{1,2} Previous studies have demonstrated that this patient population has depressed heart rate variability (HRV), indicating increased sympathetic activity, at rest\textsuperscript{1,2} as well as during sleep\textsuperscript{3} and physical exercise.\textsuperscript{4} As a result, arrhythmias are common in patients with COPD, contributing to the documented increase risk of sudden cardiac death in this chronic disease population.\textsuperscript{5–7}

The main cause of reduced HRV in patients with COPD is unclear. Plausible pathophysiologic mechanisms leading to reduced HRV in COPD include broncoconstriction,\textsuperscript{2} hypoxia,\textsuperscript{8} hypercapnia,\textsuperscript{3,7} weight loss\textsuperscript{9} and systemic inflammation.\textsuperscript{9,10} Recently, it has been suggested that cardiac autonomic function in patients with COPD is related to level of physical activity and muscle strength,\textsuperscript{11} similar to findings reported in patients with chronic heart failure.\textsuperscript{12}

Increasing COPD disease severity promotes a negative impact on exercise tolerance and magnifies the level of disability. Physical activity programs appear to safely ameliorate these COPD consequences, conferring beneficial effects on dyspnea and health-related quality of life.\textsuperscript{13,14} The positive effects of exercise training on autonomic modulation have been reported in patients with cardiac disease and may help to explain the well-documented prognostic improvement in this population.\textsuperscript{15–17} However, the effect of an aerobic exercise training program on autonomic modulation in patients with COPD has yet to be investigated. To address this gap in the literature, the aim of this study was to evaluate the impact of an aerobic exercise program on autonomic modulation in patients with moderate-to-severe COPD. We hypothesized that a six-week aerobic exercise program will improve both exercise performance and autonomic modulation in patients diagnosed with this chronic disease.

Methods

Design and study population

This is a prospective randomized controlled trial. A total of 125 patients were screened, from which forty patients of both sexes were included in the study (Fig. 1). Exclusion criteria consisted of: 1) the presence of orthopedic or neurological conditions that would preclude participation in an exercise program, 2) a history of cardiac arrhythmias or potential ECG alterations, 3) a past history consistent with heart disease, diabetes mellitus, uncontrolled hypertension, or other concomitant respiratory diseases, and 4) failure to comply with the research protocol. In this context, 85 patients were not included in the study due to concomitant ischemic cardiac disease (n = 10), diabetic neuropathy (n = 2), chronic peripheral arterial disease (n = 3), aortic aneurysm (n = 1); hypertension (n = 10), respiratory disease (associated with sequelae of tuberculosis n = 4, with bronchiectasis n = 2 and with cancer n = 2), ECG alterations (chronic atrial fibrillation (n = 4); heart block (n = 3), frequent ventricular premature beats (n = 5); musculoskeletal diseases (n = 6 with severe arthrosis of knee and hip; 1 with hip prosthesis; 5 with sequelae of stroke, 1 with Parkinson and 1 with alcoholic myopathy). In addition, 9 patients declined participation without citing a reason while the final 16 patients cited transportation issues as a primary reason for declining study participation. Patients that were included presented: 1) a diagnosis of COPD according to criteria set forth by the Global Initiative for Chronic Obstructive Lung Disease (GOLD),\textsuperscript{18} 2) compliance with medical management, 3) no change in medical management and no decompensation episodes for at least one month prior to study initiation, and 4) no participation in a regular physical exercise program for at least six months prior to study initiation.

Patients were randomly assigned to a supervised aerobic training program (TG) or to a control group (CG), without aerobic training.

All patients received regular treatment consisting of inhaled bronchodilators and steroids. None of the patients were prescribed oral steroids, antibiotics, antihypertensives or beta-blockers. The study protocol was approved by the Institutional Ethics Committee and all patients signed a written consent form prior to study initiation.

Measurements

All subjects were evaluated during the same time of the day (in order to avoid differences in response due to circadian rhythm) at an experimental room temperature of 22 °C with relative air humidity between 50% and 60%. Subjects were instructed to abstain from caffeinated and alcoholic beverages and not to perform exercise on the day before data collection.

**Lung function:** Spirometric tests were performed using a portable spirometer (Hand Held 2120, Vivalograph, Ennis, Ireland) with a calibrated pneumotachograph. Maximal inspiratory/expiratory maneuvers were performed and FEV₁, VC, FVC, FEF25-75% and maximum voluntary ventilation were determined from the best out of three trials.\textsuperscript{19} Maximal inspiratory (PImax) and expiratory pressure (PEmax) were measured using an analogic manovacumeter with a cmH₂O scale (Ger-ar; São Paulo, SP, Brazil) according to the method previously described.\textsuperscript{20}

**Cardiopulmonary exercise testing:** Incremental symptom-limited exercise test was performed in accordance with the
protocol previously described. Symptom-limited treadmill ergometric tests were performed using a computer-based ventilatory expired gas analysis system (VO2000, Medic graphics Corp., St. Paul, MN). The VO2000 uses a galvanic fuel cell for the oxygen analyzer (range 0–96%) and a non-dispersive infrared carbon dioxide analyzer (range 0–10%), both of which were calibrated prior to each exercise test as per manufacture instructions. A Pitot tube (prevent Pneumotach™, MGC) of low flow pneumotach (range 2–30 L min⁻¹) was also calibrated with a 3-L volume syringe. The flow device was connected to a buccal and the nostrils were occluded by a nose clip. Acceptable inter-day reliability for \( \dot{V}E \) (CV 7.3–8.8%) and for \( \dot{V}O_2 \), and \( \dot{V}CO_2 \) (CV 5.3–6.0%) has been evaluated in a previous study.

The following 15-s averaged ventilatory gas data were recorded: oxygen consumption (\( \dot{V}O_2 \), in mL min⁻¹ and mL kg⁻¹ min⁻¹), carbon dioxide production (\( \dot{V}CO_2 \)), minute ventilation (\( \dot{V}E \), L min⁻¹), respiratory rate (rpm), and tidal volume (VT, L). Oxyhemoglobin saturation (SpO₂, %) was determined by pulse oximetry (Nonim 8500A Plymouth, Minnesota, USA). Subjects were also asked to rate their “shortness of breath” at exercise cessation using the 0–10 Borg’s category-ratio scale; symptom scores were expressed in absolute values and corrected for exercise duration.

Capillary samples were collected from the ear lobe for blood lactate measurements (mEq L⁻¹) at exercise peak.

Six-minute walk test (6MWT): The 6MWT was performed in a 30-m corridor as described by ATS Guidelines. Dyspnea, as measured with Borg’s CR10 scale; SpO₂ and pulse rate by pulse oximetry at the start and end of the 6MWT. Two tests were performed on alternate days before treatment and the results of the second test were used given the first test tends to underestimate exercise capacity due to subject’s lack of familiarity with the procedure. Each patient was instructed to walk from one end of the corridor to the other, covering as much ground as possible during the allotted time and received standardized encouragement throughout the test.

Acquisition of \( R-Ri \) interval (\( R-Ri \)): \( R-Ri \) was registered using the Polar system at rest in both the supine (10 min) and seated position (10 min) and during the 6MWT. An elastic belt (Polar T31 transmitter, Polar Electro, Kempele, Finland) was attached to the chest of the volunteer at the level of the lower third of the sternum. The belt contains a stable case with heart rate electrodes, an electronic processing unit, and an electromagnetic field transmitter. The heart rate signals are continuously transmitted to the Polar Advantage receiver unit via an electromagnetic field. The digitally coded \( R-Ri \) length is continuously transferred to the Polar Precision Performance software that in turn displays a heart rate tachogram on the monitor.
**HRV analysis**

R–R intervals were collected during 10 min of rest and throughout the 6MWT. The sections selected for HRV analysis were deemed the most stable sections, containing 256 R–R intervals or more points in both situations. During the 6MWT, we discarded the initial 60 s of data and selected the most stable signal, corresponding to the latter portion of the test. HRV was analyzed by time (rest and exercise) and frequency domain methods (only during rest) by a specific routine developed in Matlab V. 6.1 software. In the time domain analysis, the standard deviation of the normal R–R intervals (SDNN), that is the square root of variance, and the square root of the mean sum of the squares of the difference between adjacent normal R–R intervals within a given time minus one (rMSSD) were analyzed. 26

In the frequency domain analysis, the power spectral components were reported at low (0.04–0.15 Hz) and high (0.15–0.4 Hz) frequencies using the Fast Fourier Transformation. The data, calculated by the total power less the power of the component with a frequency range between 0 and 0.03 Hz (i.e. at very low frequency), were expressed in absolute and normalized units and as a low/high frequency ratio. 26

**Exercise training program**

The 6-week physical exercise program was conducted on an outpatient basis. Aerobic exercise training consisted of stretching of lower and upper limbs and treadmill ambulation for 30 min. The training intensity on treadmill was set at 70% of the maximal speed achieved during the symptom-limited exercise test. Stretching exercises for the hamstrings, quadriceps, calves, shoulders, neck and lower back were performed before and after each session over a 10-min period. During the stretching exercises, the physiotherapist emphasized diaphragmatic breathing and awareness of proper posture in front of a mirror in the position standing and sitting. During the training sessions, the patient’s HR and SpO2 were continuously monitored. The sessions were supervised by a physical therapist, 3 times a week for the entire 6-week program. Patients were assessed at baseline and at 6 weeks. Four patients underwent the training regimen with supplemental oxygen while three patients in control group received supplemental oxygen as part of usual care. The goal was to maintain oxygen saturation >90% in both groups. Patients in the control group received no physical training, only usual care that consisted of inhalation and desobstructive maneuvers (vibration and clapping associated with postural drainage for 10 min with supported cough).

**Statistical analysis**

The statistical power analysis and sample size estimation were calculated based on standard deviation as well as the difference of HRV indices between pre and post intervention. Twenty subjects in each group was indicated as the minimum sample size required to assure adequate statistical power (80% and α = 5%). Continuous data are reported as mean and ±SD. Subjects’ characteristics and pulmonary function were compared between groups using the t-test for continuous variables and by Fisher exact test for categorical variables. Continuous variables were compared by two-way repeated measures analysis of variance. When statistical significance was detected, post-hoc testing employed the Tukey method. The relationship between the post–pre intervention change (delta) in rmSSD and 6MWT distance was assessed using Pearson’s correlation. The level of significance was set at p < 0.05. The analysis was carried out using the Statistica for Windows software release 5.1 (StatSoft, Inc, Tulsa, OK).

**Results**

**Population characteristics and pulmonary function**

Of all patients screened (125), 85 were excluded (see flowchart in Fig. 1). Forty patients were randomized to receive aerobic exercise training or usual care. However, during the study, 6 patients of control group were withdrawn from the study. Three patients were lost due to acute exacerbation of COPD, 1 died, 1 presented psychiatric problems and 1 could not undergo follow-up assessment due to newly diagnosed ischemic heart disease during the protocol. Table 1 shows that after randomization, there were no significant differences between the two groups in age, anthropometry and lung function. After the results of pulmonary function testing, patients were characterized, on average, as having moderate-to-severe airflow obstruction (FEV1: approximately 40% of the predicted value in both groups). In addition, reduced respiratory muscle

| Table 1 Age, anthropometric characteristics and lung function on baseline in COPD groups and control group. |
|------------------------|---|---|---|
| **Demographic/anthropometric** | **TG** | **CG** | **p level** |
| (n = 20) | (n = 14) |
| Age (years) | 67 ± 10 | 67 ± 10 | 0.82 |
| Gender (M/F) | 13/7 | 12/8 | 0.33 |
| Height (cm) | 161 ± 11 | 160 ± 10 | 0.66 |
| Weight (kg) | 63 ± 13 | 65 ± 16 | 0.64 |
| BMI (kg m⁻²) | 24 ± 4 | 24 ± 5 | 0.88 |
| **Pulmonary function** | | | |
| SpO₂ (%) | 91 ± 2 | 91 ± 3 | 0.64 |
| FVC (L) | 1.9 ± 0.6 | 1.8 ± 0.7 | 0.33 |
| FVC (% pred) | 64 ± 16 | 64 ± 18 | 0.93 |
| FEV₁ (L) | 0.80 ± 0.3 | 0.76 ± 0.3 | 0.67 |
| FEV₁ (% pred) | 33 ± 9 | 35 ± 11 | 0.60 |
| FEV₁/FVC | 42 ± 10 | 46 ± 12 | 0.35 |
| MIP (cmH₂O) | 44 ± 25 | 38 ± 15 | 0.43 |
| MEP (cmH₂O) | 66 ± 24 | 70 ± 23 | 0.68 |

Values expressed in mean and standard deviation. TG: training group; CG: control group; M: males; F: females; BMI: body mass index; SpO₂: peripheral oxygen saturation measured by pulse oximetry; FVC: forced vital capacity; FEV₁: forced expiratory volume in 1.0 s; MIP and MEP: maximal inspiratory and expiratory pressures; No significant differences between TG vs. CG (p > 0.05).
strength was observed in both groups. Three patients in the control group (2.6 ± 0.6 years) and four (2.9 ± 0.4 years) in the aerobic exercise group used domiciliary oxygen therapy (p > 0.05). During aerobic exercise training, patients in the experimental group were provided supplemental oxygen to maintain SpO2 ≥ 90%.

**Effects of aerobic physical exercise program on exercise capacity**

Table 2 illustrates symptom-limited exercise testing and 6MWT results. The aerobic exercise training program significantly improved (p < 0.05) peak VO2, peak heart rate, and blood lactate. In addition, at comparable submaximal exercise intensity, peak dyspnea and perceived exertion were significantly reduced following aerobic training. No significant differences in any variables were observed in control group. Moreover, participation in the aerobic exercise training program significantly improved δ6MWT distance and δrMSSD (p < 0.05). Fig. 2 shows the positive, moderate but significant correlation between δ6MWT distance and δrMSSD (r = 0.65; p = 0.001).

**Effects of the aerobic exercise training program on HRV at rest**

Table 3 shows the HRV values in time and frequency domain in both groups at rest. In the time domain analysis, the intragroup comparisons showed significant differences in rMSSD and SDNN index for the experimental group and no significant differences were observed in control group. In addition, after 6 weeks, significant differences were observed in these indexes between groups (p < 0.05). In relation to frequency domain, AF significantly increased and BF and BF/AF significantly decreased in the aerobic training group only (p < 0.05). Significant differences were only observed for the BF/AF ratio between groups after 6 weeks (p < 0.05). Delta (post-pre) of rMSSD index was comparable at rest and during exercise between groups.

Table 2  Symptom-limited exercise testing and six-minute walking test data.

<table>
<thead>
<tr>
<th></th>
<th>TG</th>
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<th>CG</th>
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<tbody>
<tr>
<td></td>
<td>(n = 20)</td>
<td></td>
<td>(n = 14)</td>
<td></td>
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<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td><strong>Maximal exercise</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Speed (km h⁻¹)</td>
<td>3.1 ± 0.9</td>
<td>4.1 ± 1.1*</td>
<td>3.1 ± 0.9</td>
<td>3.2 ± 1.0†</td>
</tr>
<tr>
<td>VO2, % pred</td>
<td>58 ± 19</td>
<td>68 ± 20*</td>
<td>63 ± 20</td>
<td>64 ± 21</td>
</tr>
<tr>
<td>VO2, L</td>
<td>0.854 ± 0.19</td>
<td>1.00 ± 0.24*</td>
<td>0.866 ± 0.21</td>
<td>0.861 ± 0.11</td>
</tr>
<tr>
<td>VO2, mL kg⁻¹ min⁻¹</td>
<td>14 ± 2.2</td>
<td>16 ± 2.8*</td>
<td>14 ± 3.8</td>
<td>13 ± 4.7</td>
</tr>
<tr>
<td>VCO2, mL min⁻¹</td>
<td>0.947 ± 0.3</td>
<td>1.01 ± 0.38</td>
<td>0.961 ± 0.4</td>
<td>1.02 ± 0.28</td>
</tr>
<tr>
<td>RQ</td>
<td>1.13 ± 0.4</td>
<td>1.00 ± 0.2</td>
<td>1.07 ± 0.3</td>
<td>1.17 ± 0.3†</td>
</tr>
<tr>
<td>VE, L min⁻¹</td>
<td>29 ± 5.6</td>
<td>31 ± 6.5*</td>
<td>29 ± 5.7</td>
<td>29 ± 6.2</td>
</tr>
<tr>
<td>Respiratory rate, breaths min⁻¹</td>
<td>32 ± 5</td>
<td>27 ± 3*</td>
<td>31 ± 5</td>
<td>30 ± 5†</td>
</tr>
<tr>
<td>Tidal volume, L</td>
<td>0.932 ± 0.26</td>
<td>1.17 ± 0.31*</td>
<td>0.946 ± 0.18</td>
<td>0.966 ± 0.20†</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>112 ± 13</td>
<td>123 ± 13*</td>
<td>112 ± 14</td>
<td>114 ± 14</td>
</tr>
<tr>
<td>Blood lactate, mMol L⁻¹</td>
<td>1.6 ± 0.5</td>
<td>1.9 ± 0.4*</td>
<td>1.6 ± 0.8</td>
<td>1.5 ± 0.5†</td>
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<tr>
<td><strong>Submaximal exercise</strong></td>
<td></td>
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<tr>
<td>Dyspnea</td>
<td>6.0 ± 1.7</td>
<td>4.6 ± 1.6*</td>
<td>6.0 ± 2.0</td>
<td>5.8 ± 1.8†</td>
</tr>
<tr>
<td>Leg effort</td>
<td>5.4 ± 1.1</td>
<td>4.3 ± 1.0*</td>
<td>6.3 ± 2.6</td>
<td>6.2 ± 2.3†</td>
</tr>
<tr>
<td>Walking distance, m</td>
<td>381 ± 87</td>
<td>487 ± 85*</td>
<td>393 ± 96</td>
<td>406 ± 102†</td>
</tr>
<tr>
<td>rMSSD (ms)</td>
<td>6.8 ± 3.5</td>
<td>13.7 ± 4.0*</td>
<td>6.2 ± 2.8</td>
<td>5.9 ± 3.7†</td>
</tr>
</tbody>
</table>

Values expressed in mean and standard deviation. TG: training group; CG: Control group; rMSSD: square root of mean of the squared differences between adjacent R–R intervals.

*Significant differences between before and after 6 weeks (p < 0.05).
†Significant differences after 6 weeks between TG vs. CG (p < 0.05).
Participation in aerobic exercise training was, however, associated with a greater increase in rMSSD index at rest and exercise \( (p < 0.05) \).

**Discussion**

In this randomized clinical trial we were able to demonstrate that whole-body physical training produced significant improvements in submaximal and maximal exercise capacity in patients with COPD. In addition, this is the first study, to our knowledge, that compared the positive effects of 6 weeks of aerobic exercise training on heart rate variability during rest and exercise in a cohort diagnosed with this chronic disease. These results potentially have a high level of clinical relevance given that disorders of cardiac autonomic control have been associated with the development of arrhythmias\(^6,7\) and sudden death\(^5,27\) in the COPD population. In this context, HRV may prove valuable in evaluating disease severity\(^28\), assessing risk for future adverse events and evaluating the positive physiologic effects of different therapeutic interventions\(^21,29\) such as aerobic exercise training. Future research in this area is needed to address these issues and more firmly establish the importance of HRV assessment in this chronic disease population.

**Effects of aerobic exercise training on submaximal and maximal performance**

In the present study we observed that 6 weeks of aerobic exercise training improved submaximal and maximal exercise performance as well as physiological data in COPD patients (Table 2). Consistent with our results, other groups have reported that aerobic exercise training is essential in all stages of COPD.\(^{13,14}\) This form of training can reduce dyspnea, improve functional capacity and quality of life in these patients. In addition, aerobic exercise training, applied 3 times a week can provide beneficial physiological adaptations in COPD patients.\(^{13,14,18,21}\)

A primary novel finding of the present study was a significant improvement of walking distance and rMSSD in these patients after physical training and moderate significant association between delta of walked distance and rMSSD index (Fig. 2). This finding is not particularly surprising given that aerobic exercise training has likewise been shown to improve parasympathetic activity in patients diagnosed with cardiovascular disease\(^15,16\) as well as elderly sedentary subjects who are apparently healthy.\(^30\) In this context, good aerobic fitness has been suggested to be associated with increased HRV, most likely attributed to increased vagal activity in the control of heart rate. In accordance with these findings, we only observed a significant increase in peak VO\(_2\) in COPD subjects undergoing exercise training with no adaptations in the control group.

**HRV in COPD patients before and after physical training**

In the present study, we observed that COPD patients before physical training showed markedly higher levels of sympathetic activity at rest (Table 3) compared with previously reported normal HRV values.\(^26\) Previous study has reported that patients with COPD present with reduced HRV during rest\(^1-3\) and exercise.\(^4\) However, the main cause

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Time domain</th>
<th>Frequency domain</th>
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<tbody>
<tr>
<td></td>
<td>TG (n = 20)</td>
<td>CG (n = 14)</td>
</tr>
<tr>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>rMSSD (ms)</td>
<td>10.1 ± 4.6</td>
<td>19.2 ± 4.9*</td>
</tr>
<tr>
<td>rMSM (ms)</td>
<td>14.6 ± 6.2</td>
<td>24.8 ± 6.9*</td>
</tr>
<tr>
<td>LF (nu)</td>
<td>0.69 ± 0.14</td>
<td>0.47 ± 0.15*</td>
</tr>
<tr>
<td>HF (nu)</td>
<td>0.31 ± 0.1</td>
<td>0.53 ± 0.15*</td>
</tr>
<tr>
<td>LF/HF</td>
<td>3.1 ± 2.3</td>
<td>1.1 ± 0.8*</td>
</tr>
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</table>

Values expressed in mean and standard deviation. TG: training group; CG: control group; rMSSD: square root of mean of the squared differences between adjacent R–R intervals; rMSM: standard deviation of R–R intervals; LF (nu): low frequency in normalized units; HF (nu): high frequency in normalized units; and LF/HF: low frequency/high frequency ratio.

*Significant differences between before and after 6 weeks \( (p < 0.05) \).

†Significant differences after 6 weeks between TG vs. CG \( (p < 0.05) \).

![Figure 3](image-url) Delta of effects of the aerobic exercise training program at rest and during the 6MWT in both groups. Note: Only patients in the TG demonstrated a significant improvement in rMSSD at rest and during exercise in the follow-up assessment. * Significant differences between TG (in gray) vs. CG (in black), \( p < 0.05 \).
of this autonomic disorder is not clear, although some plausible hypotheses have been posited. Chen et al. reported that reduced HRV is associated with hypoxemia in patients with COPD. In this context, some studies have been conducted to test the use of oxygen supplementation in these patients. The main finding of these studies is that supplemental oxygen could partially reverse autonomic nervous system dysfunction in COPD. Other investigators have focused on the relationship between COPD severity and reduced HRV. Pagani et al. observed a significant association between HRV indexes and FEV1. In contrast, Chhabra and De reported that cardiovascular autonomic neuropathy is present in mild as well as moderate-to-severe COPD. Similarly, we demonstrated that alterations of autonomic balance are more prevalent in hypoxemia but also occur in normoxemic patients. In the present study, we assessed the effects of aerobic exercise training in COPD patients with or without hypoxemia. Only four patients were, however, trained with oxygen. The effects of oxygen therapy on improvement in HRV at rest and during exercise could therefore not thoroughly be explored. Based on our findings, it is likely that the positive adaptations brought about by aerobic exercise training played a significant contributory role.

More recently, other investigators have demonstrated that cardiac autonomic function of patients with COPD is not associated with disease severity, but rather the level of physical activity in daily life. In this context, previous studies have reported that aerobic exercise training was associated with improvement of HRV in healthy elderly and chronic disease cohorts. In the present study, we observed a significant improvement in parasympathetic activity and reduction of sympathetic activity at rest and during submaximal exercise after 6 weeks of aerobic exercise training. A possible explanation for these results is that the training program employed in the present investigation may have reduced sympathetic activity by reducing anxiety, and/or catecholamine levels, although these mechanisms remain speculative at this time.

Following aerobic exercise training, the present study also found a reduction in respiratory rate (RR) and an increase in tidal volume (TV) during exercise (Table 2). Other investigators have found that RR reduction and TV increase can modulate HRV, mainly improving parasympathetic activity in the control of heart rate. These adaptations in ventilatory mechanics with our intervention may also serve as a mechanism for the demonstrated improvement in autonomic modulation. Moreover, the observed significant reduction in dyspnea may also be related to the favorable adaptations in RR and TV.

Another possible explanation for the reduction in sympathetic activity at rest and during exercise after aerobic training is due to adaptations in the peripheral musculature. Heindl et al. observed that COPD patients presented with higher muscle sympathetic nerve activation compared with healthy subjects. Ischemic metabolites generated during muscle contraction have been shown to stimulate local receptors and cause increases in heart rate, arterial pressure and sympathetic activity. In addition, the increased work of breathing in these patients could lead to sympathetic activation through stimulation of local metaboreceptors. The positive adaptations brought about by aerobic exercise training may help to reverse these abnormalities.

Finally, lung inflation reflexes can modulate the influence of vagal modulation on heart rate. Dynamic hyperinflation is common in COPD patients and negatively impact hemodynamic adjustments. In the present study, we observed that RR reduced after physical training, concomitantly with reduction in dyspnea and improvement in TV. These adjustments in the respiratory pattern may again help to explain the improvement of parasympathetic activity after training.

In conclusion, this randomized clinical trial demonstrates that a 6-week aerobic exercise training program leads to an improvement in exercise tolerance, promotes ventilatory and physiological adaptations and favorably impacts the derangements in autonomic modulation of heart rate both at rest and during exercise in patients with COPD.

Acknowledgments

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Conflict of interest statement

The authors declare that they have no conflicts of interest related to the present study.

References